MATTERS ARISING

Exposure to chemicals and systemic sclerosis

Occupational exposure to various chemicals, including vinyl chloride, silica dust, epoxy resin, benzene, trichloroethylene, perchloroethylene, and other solvents, has been described as a potential provoking factor of systemic sclerosis (SSc) and scleroderma like disorders.[1] However, the precise contribution made by occupational environmental factors to the occurrence of scleroderma remains unknown.[2]

Susceptibility to these agents may differ widely in distinct areas of Europe, as a result of both genetic and environmental differences, as the following examples indicate.

Several cases of exposure to solvents have been described, including that reported by Garcia-Zamalloa and colleagues in the *Annals*.[3] Predominantly male workers have been described,[4 5] except in the study by Yamakage and Ishikawa.[6] In the Hungarian population, a remarkable predominance of women has been found among patients with SSc who were previously exposed to chemicals:[7 8] 23 of our 180 patients with SSc had exposure to solvents in their case history; only three of them were men. During the epoch of 'socialist industrialisation' in the 1950s and 60s, a large number of unskilled female workers from rural areas were employed to do menial jobs in the urban areas, with a concomitant higher risk of exposure to solvents and other chemicals. After a latent period of several years, these patients developed SSc indistinguishable from 'true' systemic sclerosis. Now, with the improvement of working conditions in Hungary, the number of cases with exposure to chemicals seems to be decreasing.

Vinyl chloride disease seems to be relatively frequent among British workers exposed to this agent.[9 10] Conversely, in Hungary, vinyl chloride disease has been found to be extremely rare, in spite of the presence of well detectable exposure to this chemical: 464 workers were exposed to vinyl chloride in Kazincbarcika (north eastern Hungary) for more than 10 years on average, but only one case of vinyl chloride disease has been described, despite regular and well documented screening for the presence of this disorder. Another group of 60 workers has long been exposed to trichloroethylene without any signs of scleroderma related disease.

Genetic markers are useful tools for relating chemically induced SSc-like vinyl chloride disease.[9] Susceptibility to this disorder is increased in the presence of HLA-DR5 or a gene in linkage disequilibrium with it and an antigen associated with the haplotype A1 B8, while DR3 favours the progression of the disease,[10] as seen among the British workers.

The heterogeneity of clinical symptoms, distribution of major histocompatibility complex alleles, and autoantibody profiles in SSc suggest that this disorder may represent a group of distinct diseases, and that the characteristic genetic and environmental predisposing risk factors can be totally different in these subgroups. The environmental contribution to scleroderma is unknown, raising the need for a European multicentre case-control study to determine the groups at risk.

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1 Silman A J. Epidemiology of scleroderma. *Ann Rheum Dis* 1991; **50** (suppl 4): 846–53.
2 Silman A J, Jones S. What is the contribution of occupational environmental factors to the occurrence of scleroderma in men? *Ann Rheum Dis* 1992; **51:** 1322–4.
3 Garcia-Zamalloa A M, Ojeda E, Gonzales-Beneitez C, Goni J, Garrido A. Systemic sclerosis and organic solvents: early diagnosis in industry. *Ann Rheum Dis* 1994; **53:** 618.
4 Bottomley W W, Sheehan Dare R A, Hughes P, Cunliffe W J. A sclerodermatous syndrome with unusual features following prolonged occupational exposure to organic solvents. *Br J Dermatol* 1993; **128:** 203–6.
5 Brasington R D J, Thorpe Swenson A J. Systemic sclerosis associated with cutaneous exposure to solvent: case report and review of the literature. *Arthritis Rheum* 1991; **34:** 631–3.
6 Yamakage A, Ishikawa H. Generalized morphea-like scleroderma occurring in people exposed to organic solvents. *Dermatologica* 1982; **165:** 186–93.
7 Czirják L, Bokk A, Csontos G, Lôrincz G, Szegedi G. Clinical findings in 61 patients with progressive systemic sclerosis. *Acta Derm Venereol Stockh* 1989; **69:** 533–6.
8 Czirják L, Nagy Z, Szegedi G. Survival analysis of 118 patients with systemic sclerosis. *J Int Med* 1993; **234:** 335–7.
9 Black C, Briggs D, Welsh K. The immunogenetic background of scleroderma—an overview. *Clin Exp Dermatol* 1992; **17:** 73–8.
10 Black C, Pereira S, McWhirter A, Welsh K, Laurent R. Genetic susceptibility to scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. *J Rheumatol* 1986; **13:** 1059–62.

LETTERS TO THE EDITOR

Acquired sideroblastic anaemia associated with penicillamine therapy for rheumatoid arthritis

Penicillamine has been successfully used in the treatment of rheumatoid arthritis since 1964.[1 2] Most of the serious reactions have been haematological and include agranulocytosis, thrombocytopenia, and aplastic anaemia.[2-5] The incidence of some adverse side effects, such as thrombocytopenia, rashes and proteinuria, has been shown to be unacceptably high with high dose treatment.[4]

We report a case of acquired sideroblastic anaemia following treatment with penicillamine for rheumatoid arthritis.

A 50 year old man with a five year history of rheumatoid arthritis and non-insulin-dependent diabetes mellitus developed more active joint disease associated with rheumatoid nodules and erosive changes revealed by radiography. His joint disease had been controlled on ibuprofen 600 mg three times daily, but in June 1988 penicillamine 125 mg once daily was added to his regimen. The dose was gradually increased, by 125 mg at monthly intervals, to 500 mg once daily. At no stage was he taking phenacetin or paracetamol.

Before he commenced taking the penicillamine, the patient's full blood count had been stable, with a haemoglobin concentration of 13·2 g/dl, platelet count 351×10^9/l, leucocyte count $9{\cdot}3 \times 10^9$/l and erythrocyte sedimentation rate 35 mm/1st h. The film was mildly microcytic (mean cell volume (MCV) 76 fl) and hypochromic. The white cell differential was normal.

Two months after he started treatment, his haemoglobin had decreased to 9·9 g/dl and showed hypochromia and microcytosis (MCV 68 fl). He then began a course of iron therapy and the haemoglobin temporarily increased to 12 g/dl in November 1988. By January 1989 his haemoglobin decreased again, to 10·8 g/dl with a hypochromic, microcytic picture (MCV 70 fl) and by February 1989 it had decreased further, to 7·0 g/dl. At this stage, the film showed a dimorphic picture with some hypochromia, basophilic stippling, and poikilocytosis. There were some nucleated red cells and the white cells and platelets were normal. Because of the appearance of the blood film, the possibility of sideroblastic anaemia was raised.

Clinically, there was no evidence of blood loss and an endoscopy was normal. His arthritis was considered to be well controlled on therapy, with a C reactive protein 29 mg/l (normal range (NR) < 20 mg/l) and C3 degradation product 15 U/ml (NR 5–12 U/ml); vitamins B-12 and folate levels were normal, serum iron 33 μmol/l (NR 14–34 μmol/l), and iron binding capacity 34 μmol/l (NR 43–72 μmol/l). Bone marrow aspirate and trephine revealed a hypocellular marrow with markedly reduced erythropoiesis, gross dyserythropoiesis and 24% ringed sideroblasts. The karyotype was normal. The appearance of the myeloid and megakaryocytic series were normal. During the period of investigation the haemoglobin decreased to a minimum of 4·9 g/l. The patient's penicillamine regimen was discontinued and he began taking pyridoxine 100 mg twice daily. He required a blood transfusion to control his symptoms, but subsequently maintained his haemoglobin at about 12·5 g/dl, with a normal MCV (81 fl). A repeat bone marrow aspirate at two months was hypercellular, and although there was mild dyserythropoiesis, ringed sideroblasts were not present.

During subsequent follow up, the patient's joint disease flared. In view of the previous problem, it was decided initially to treat him with prednisolone 5 mg once daily and, more recently, with hydroxychloroquine.

Patients with acquired idiopathic sideroblastic anaemia show abnormalities of all three haemopoietic cell lines. The changes are most marked in the red cell lineage, with at least 15% of nucleated erythroid cells in the marrow being ringed sideroblasts.[6] The peripheral blood shows a dimorphic picture with poikilocytosis, basophilic stippling and some hypochromic features, although the overall MCV is often slightly increased. The karyotype may be abnormal and there is a predisposition to develop acute leukaemia.[6]

Secondary sideroblastic change occurs in a wide variety of conditions, but the number of

ringed sideroblasts is generally many fewer than 15%. The white cell and megakaryocyte series are not affected. Occasionally, patients develop severe sideroblastic anaemia secondary to drug therapy or severe alcohol abuse which may reverse on stopping the offending drug.[7-9] In the case of isoniazid, the mechanism is thought to be inhibition of pyridoxine related haemsynthesis; isoniazid binds pyridoxine and the complex is excreted via the kidney.[9] Penicillamine may have a similar mode of action.[10]

A number of haematological side effects of penicillamine therapy have been reported. Sullivan *et al*[10] reported a case of sideroblastic anaemia in a patient with biliary cirrhosis who was taking 1000 mg of penicillamine a day. The features of sideroblastic anaemia developed over 12 months and resolved after cessation of penicillamine and introduction of pyridoxine treatment. The patient later recommenced taking penicillamine with pyridoxine cover, without further problems. This patient had abnormal liver function and this may have contributed to the situation.

Ramselaar *et al*[8] reported a patient who developed aplastic anaemia secondary to penicillamine. The leucopenia resolved, but the patient remained anaemic and thrombocytopenic with bone marrow features of sideroblastic anaemia. The patient did not respond to pyridoxine therapy and subsequently died of a septicaemic episode.

In our patient, the development of sideroblastic anaemia was closely associated with the introduction of penicillamine therapy and his rheumatoid arthritis was relatively quiescent as judged by clinical and laboratory parameters. On introduction of pyridoxine, the patient's anaemia resolved and the abnormal sideroblasts disappeared from the bone marrow. Thus the sudden onset of anaemia and the response to withdrawal of penicillamine strongly implicate penicillamine as the causal agent. The follow up bone marrow analysis showed only minor dysplastic features—a frequent finding in pyridoxine sensitive sideroblastic anaemia.

We believe that this is the first reported case of acquired sideroblastic anaemia which was reversible with pyridoxine, in a patient with rheumatoid arthritis. As many of the adverse effects of penicillamine are dose dependent,[4] it may be possible to reintroduce penicillamine under pyridoxine cover, particularly if a smaller dose controls the joint disease.

This report highlights the need for vigilance in patients with rheumatoid arthritis who are receiving maintenance penicillamine. The development of anaemia whilst on penicillamine treatment warrants careful investigation, including consideration of a bone marrow aspirate if other more common causes are excluded.

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1 Jaffe I A. Rheumatoid arthritis with arteritis—a report of a case treated wtih penicillamine. *Ann Intern Med* 1964; **61**: 556–63.
2 Multicentre Trial Group. Controlled trial of D-penicillamine in severe rheumatoid arthritis. *Lancet* 1973; **1**: 275–80.
3 Weiss A S, Markenson J A, Weiss M S, Kammerer W H. Toxicity of D-penicillamine in rheumatoid arthritis. *Am J Med* 1978; **64**: 114–20.
4 Hill H F H. Penicillamine in rheumatoid arthritis: adverse effects. *Scand J Rheumatol Suppl* 1979; **28**: 94–9.
5 Kay A G L. Myelotoxicity of D-penicillamine. *Ann Rheum Dis* 1979; **38**: 232–6.
6 Bennett J M, Catovsky D, Daniel M T, *et al.* (The French-American-British Group). Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982; **51**: 189–99.
7 Verwilghen R, Reybrouck G, Callens L, Cosemans J. Antituberculous drugs and sideroblastic anaemia. *Br J Haematol* 1965; **11**: 92–8.
8 Ramselaar A C P, Dekker A W, Huber-Bruning O, Bijlsma J W J. Acquired sideroblastic anaemia after aplastic anaemia caused by D-penicillamine therapy for rheumatoid arthritis. *Ann Rheum Dis* 1987; **46**: 156–8.
9 Hines J D. Reversible megaloblastic and sideroblastic marrow abnormalities in alcoholic patients. *Br J Haematol* 1969; **16**: 87–101.
10 Sullivan A C, Burakoff R, Weintraub L R. Sideroblastic anaemia associated with penicillamine therapy. *Arch Intern Med* 1981; **141**: 1713–4.

Homozygous complement factor deficiency and primary antiphospholipid syndrome: a clinical and serological study

Complement factor 2 (C2) deficiency is the most common inherited complement deficiency.[1] In 60% of cases the disorder is associated with a lupus-like disease, and to a lesser extent with recurrent bacterial infections. An isolated form of glomerulopathy is described in about 25% of patients.[2] Here, we describe a patient with homozygous C2 deficiency and primary antiphospholipid syndrome (PAPS). The main PAPS manifestation was repeated cerebrovascular disease; another relevant feature was hypertensive nephropathy without overt nephritis.

Bilateral cataracts were diagnosed in a 40 year old man in 1986; simultaneously, he was discovered to be hypertensive. There was no previous history of renal calculus or urinary symptoms. Blood analysis revealed creatinine 0·247 mmol/l, urea 27·8 mmol/l, triglycerides 226 mg/dl as the only altered parameters. Urinary sediment was normal; protein excretion was 0·2 g/24 h. The patient was treated with captopril 50 mg/day, with good blood pressure control.

Nine months later, the patient suffered a convulsive seizure without any residual neurological deficit.

Laboratory studies showed low haemolytic complement activity (< 8 U/ml) with normal C3 and C4 concentrations. Antinuclear antibodies and antibodies to double stranded DNA, extractable nuclear antigens and rheumatoid factor were negative.

A percutaneous renal biopsy showed a segmental and focal glomerulosclerosis, without acute occlusive changes by fibrin thrombi or fibrinoid necrosis of the vessel wall. Immunofluorescence showed a weak positivity with IgA, C3, C4, and Clq antisera.

In 1987, the bilateral cataracts were surgically removed. Subsequently, the patient became aware of a right visual field defect.

Three years later (May 1990) he showed clinical features of intermittent claudication with inadequate blood supply to the lower extremity. In July 1990 he suddenly experienced dysarthria, right dismetria and lateropulsion with mild right hemiparesis and hemihypoaesthesia. A right homonymous hemianopsia, matching the earlier visual complaint, was also detected. Antiplatelet drug treatment (aspirin) was started. Cranial computed tomography, performed 72 hours afterwards, showed a recent right cerebellar hemisphere infarct and an old left occipital lobe infarct. Angiographic examination showed abnormally dilated basilar and left vertebral arteries.

At this stage, anticardiolipin antibodies were detected by standard enzyme linked immunosorbent assay.[3] Their values were moderate positive for IgM and low positive for IgG (according to the international standards for that assay[3]); a year later IgG and IgM values were both moderate positive. Coagulation studies showed normal prothrombin time and activated partial thromboplastin time. Thrombocytopenia was not found. HLA typing was performed using microlymphocytotoxicity, and complotypes assayed: agarose electrophoresis, immunofixation and Coomassie staining for C4; cellulose acetate electrophoresis, immunofixation and nigrosin staining for factor B; and polyacrylamide isoelectrophoresis, immunofixation and silver staining for C2. The total haemolytic complement activity and C2 were undetectable, with normal C3 and C4 concentrations (table). Reconstitution of total haemolytic complement activity was possible by addition of C2. The results of complotype and haplotype analysis were also compatible with homozygous C2 deficiency (table).

The proband had a sister who suffered repeated migraines and died at the age of 30 years from cardiac infarction; the father also died (aged 64 years) from cardiac infarction. The mother was asymptomatic and had negative autoimmune serology.

We present here the first description (*Medline* 1987–April 94) of a patient with a homozygous C2 deficiency and PAPS. C2 deficiency is a molecular genetic deficiency with two variants;[4] in the proband, the HLA haplotype corresponded with the type I form, although the complotype was not typical.

Immunochemical concentrations of components of the complement system, classical haemolytic complement activity (CH_{50}) and class I, II, and III specificities in the family members

Component	*Family member*		*Normal range*
	Mother	*Proband*	
CH_{50} (U/ml)	138	0	100–180 U/ml
C2 (mg/dl)	1·9	0	1·5–5·7 mg/dl
C3 (mg/dl)	85	90	80–120 mg/dl
C4 (mg/dl)	39	41	20–40 mg/dl
HLA phenotype			
Class I	A2, A25, B7, B18	A25, A–, B18, B–	
Class II	DR2, DR4, DQw1, DQw3	DR2, DR–, DQw1	
Class III	C2*C, C2*Q0	C2*Q0, C2*Q0	
	Bf*S, Bf*S	Bf*S, Bf*S	
	C4A*3, C4A*3	C4A*3, C4A*3	
	C4B*1, C4B*2	C4B*2, C4B*2	